Stage of the Formation of the Human Upper Lip

By

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Introduction

Since the so-called classical descriptions by Dursy and His at the end of the last century, the normal and abnormal development of the upper lip has been studied in human or mammalian embryos by many investigators: Frazer (1911); Maurer (1936); Veau (1938); Hoepke and Maurer (1938); Ströer (1939); Streeter (1948); Tondury (1950, 1961); Politzer (1952); Stark (1954, 1961); Stark and Ehmann (1958); Patten (1953, 1961); Warbrick (1960); Smith and Monie (1969). These works have dealt almost exclusively with the general pattern of the development of upper lip and the pathogenesis of cleft lip. We have as yet very little information as to the timing when the human upper lip is normally differentiated.

On the other hand, there is a problem of how to identify cleft lip at its initiating stage in the course of examining a large number of human embryos for the presence of the anomaly, for there may be a possibility that some cases of upper lip which are unusually retarded in differentiation are incorrectly diagnosed as cleft lip. Thus, the norm for the developmental stage of upper lip must be established for the determination of the defect at its initiating stage.

It may be thought that there exist individual variations and side differences in the development of upper lip. Therefore, investigation for the upper lip development in a fairly number of specimens may be essential in order to establish the standard for the developmental stage of upper lip.

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In our laboratory, a large number of human embryos fixed immediately after induced abortions have been stored. This paper is designed to determine the precise time range of the development of the human upper lip, to elucidate the side difference of upper lip in development, and to settle one of the criteria for the identification of cleft lip at its initiating stage on the basis of the observation of the human embryonic specimens selected from the collection in our laboratory.

Materials and Methods

Human embryos used for the present study were obtained from mothers whose pregnancies were interrupted by curettage or induced abortion for socioeconomical reasons. Details of the source of the materials were reported elsewhere (Nishimura et al., 1968). The embryos were carefully washed with saline solution to remove maternal blood coagula and fixed in Bouin's fluid at the clinic of collaborating obstetricians for storage.

The embryos were carefully examined under the binocular stereomicroscope to determine the developmental horizon using Streeter's criteria (1942, 1945, 1948, 1951). The preliminary study by the observation of the embryos at horizons ranging from XV to XXIII (approximately at 5 to 7 weeks of age) showed that the stage of the organogenesis of upper lip lay between horizon XVI and XX. The 113 specimens included in this range were used for this study.

Observation for the evaluation of the developmental stage of upper lip was systematically made under the binocular stereomicroscope: the upper lip region of each embryo was examined at the caudal two thirds point of total length of the future upper lip, to identify the rostrocaudal sequence of the merging between the medial nasal processes and maxillary processes on each side. After these procedures, some of the specimens at each horizon were embedded in paraffin, serially sectioned at 6 to 10 microns thick transversely in the region of upper lip and stained with hematoxylin and eosin.

Observations

The various stages of the development of upper lip were noticeable among those embryos at horizons ranging from XVI to XX. Therefore, according to the degree of development, developmental stages of upper lip were divided into 5 ones as follows:

Stage I shows that the rostro-caudal merging between the medial nasal and maxillary processes has not occurred or not reached over two thirds of total length of the future upper lip
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Stage II shows that the merging has occurred over two thirds of total length of the future upper lip on either side (right or left).

Stage III represents that the merging has completed over the two thirds of total length of the future upper lip on both sides, although the boundary grooves between the processes are still deep and can be easily recognized.

Stage IV is in that the grooves are less distinct than in the previous stage and hardly traceable.

Stage V has the almost completely developed upper lip with the boundary grooves disappeared.

The distribution of the embryos at each of the above mentioned stages among each horizon group is presented in Table 1. The more detailed findings will be described below. The standard contours of the upper lip in development at each horizon are shown in Fig. 1-5.

Embryos at horizon XVI (Fig. 1)

At this horizon, 14 embryos were studied, in which 2 embryos had reached more advanced stage of development of facial region than the others. In those 2 embryos, the various facial processes were well differentiated and easily distinguished around the stomatodaeum. The contact between the maxillary and medial nasal processes was observed on both sides. It was only these 2 cases that the rostrocaudal merging between the both processes had initially occurred, but the extent of the merged part did not exceed the two thirds of the total length of the future upper lip, and the boundary grooves between the maxillary and medial nasal processes did not still disappear. These 2 specimens belonged to Stage I (Table 1).

In the other 9 specimens, the outline of the facial region offered no indication of the future appearance of the face. The various

<table>
<thead>
<tr>
<th>Horizon (Streeter)</th>
<th>No. of cases examined</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
<th>Stage V</th>
<th>Labio-dental groove</th>
</tr>
</thead>
<tbody>
<tr>
<td>H:16</td>
<td>14</td>
<td>11</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>H:17</td>
<td>16</td>
<td>7</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>H:18</td>
<td>31</td>
<td>2</td>
<td>1</td>
<td>9</td>
<td>9</td>
<td>10</td>
<td>29</td>
</tr>
<tr>
<td>H:19</td>
<td>40</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>38</td>
<td>9</td>
</tr>
<tr>
<td>H:20</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>113</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
facial processes were present around the wide opening of the stomatodaeum, that is, laterally the paired maxillary and rostrally the paired medial nasal processes, although they were relatively small and not so prominent. The boundaries between the processes were formed by shallow groove. Both the maxillary and medial nasal processes did not so differentiate to contact with each other. This group also belonged to Stage I (Table 1).

The other 3 cases showed the side difference in the extent of the merging between the maxillary and medial nasal processes (Table 2). In these cases the both processes had relatively well advanced in differentiation as compared with the other 9 specimens described above, but the merging between the processes was more retarded on the left side in 2 cases and on the right side in one case than on the opposite respectively. These cases were included in Stage II (Table 1).

Any specimens at this horizon did not show the upper lip as a separate structure.

Embryos at horizon XVIII (Fig. 2)

All of the facial processes differentiated well with definite boundary grooves between them among almost all cases of 16 specimens at this horizon. The degree of them in development belonged to the range from Stage I to III. The caudal end of the medial nasal processes, which was named the grobular process of His, became remarkably enlarged in all cases.

The nasal pits, which were laterally located with wide distance from each other on the ventral aspect of the face in the previous horizon, were closer together and increased in their depth.

Only 6 cases out of 16 embryos at this horizon were in Stage III, but they showed no evidence of the upper lip as a separate structure.

### Table 2. Developmental stage and side difference of differentiation of upper lip

<table>
<thead>
<tr>
<th>Horizon (Streeter)</th>
<th>No. of cases examined</th>
<th>Both processes* non-fused</th>
<th>Both processes** fused</th>
</tr>
</thead>
<tbody>
<tr>
<td>H:16</td>
<td>14</td>
<td>R. 1 L. 2 R. + L. 11</td>
<td>R. + L. 0</td>
</tr>
<tr>
<td>H:17</td>
<td>16</td>
<td>3 0 7</td>
<td>6</td>
</tr>
<tr>
<td>H:18</td>
<td>31</td>
<td>0 1 0</td>
<td>28</td>
</tr>
<tr>
<td>H:19</td>
<td>40</td>
<td>0 0 0</td>
<td>40</td>
</tr>
<tr>
<td>H:20</td>
<td>12</td>
<td>0 0 0</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>113</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The case without fused part over 2/3 of total length of future upper lip
** The case with fused part over 2/3 of total length of future upper lip
As shown in Table 2, the side difference in development was observed in 3 cases (Table 2).

Embryos at horizon XVIII (Fig. 3)

The specimens at this horizon showed the wide variation in the degree of development of upper lip. The stages ranged from I to V. The specimens included in the later stage (Stage IV and V) were 19 cases out of 31 embryos (Table 1). In those specimens the boundary grooves between the medial nasal and maxillary processes were becoming indistinct or almost vanished.

The remarkable change in development was observed in two embryos in Stage V, that is, there was evidence of the labio-dental groove at the lateral-posterior region of maxillary processes on the palatal view (Table 1). In this stage there was a little indication of the future appearance of upper lip, although the median-caudal portion of the embryonic lip still showed smooth concavity. The side difference in upper lip development was found in one case (Table 2).

Embryos at horizon XIX (Fig. 4)

The distribution of the 40 embryos at this horizon by developmental stage of upper lip was limited in Stage IV and V. The boundary grooves between the facial processes completely disappeared in almost all cases. The labio-dental groove appeared in 31 cases (Table 1), and it separated the upper lip as independent structure. The central-caudal portion of the upper lip showed a slight concavity or had almost flattened surface.

Embryos at horizon XX (Fig. 5)

In all the specimens at this horizon, the labio-dental groove increased in its depth (Table 1), and the upper lip could be recognized as a definite structure. The side difference in development was not observed in any case as presented in Table 2.

Discussion

In the present investigation, observation of the development of the human upper lip in its critical stage reveals that the formation of the upper lip takes place in the period between horizon XVI to XX and shows that the great part of the embryonic upper lip is completely differentiated at horizon XIX in almost all cases and over horizon XX in all cases.

The merging between the medial nasal and maxillary processes begins to occur at horizon XVI and progresses in its extent mainly at the stage between horizon XVII and XVIII, which is probably a
critical period in the formation of bilateral or unilateral cleft lip.

According to the descriptions of the development of upper lip by Streeter (1948), the upper lip was not differentiated as a separate structure in his embryos at horizon XVIII and suggested that the complete differentiation of the lip might be in the more later stage of development. His descriptions in horizon XVIII are essentially coincident with the present results. However, in this study, the wide variation in the degree of development of upper lip have been observed in the specimens especially at this horizon. Several specimens showed the more differentiated upper lip than those described by Streeter.

In 1960, Warbrick studied 15 human materials ranging in size from 7 to 22 mm crown-rump length. He stated in the description of the 16 mm embryo, "the separation of the upper lip from the rest of the upper jaw region has not yet commenced, and there is no evidence of the labio-dental groove", and he observed the differentiation of the upper lip and the groove in a 22 mm C-R length embryo. These descriptions were compared with the present results by reference to the data on the developmental horizon correlated with crown-rump length established by our group (Table 1 in Nishimura et al., 1968) and it was thought that his descriptions were approximately coincident with that noted by the present author.

The side difference in development of upper lip was observed in the stages at horizon XVI, XVII and XVIII as presented in Table 2, which showed no consistency among them. On the other hand, as noted in several literatures (Kobayashi, 1958; Fraser and Calnan, 1961; Greene et al., 1964; Ingalls et al., 1964; Moller, 1965), unilateral cleft lip is more frequent on the left side among infants. There has been no satisfactory explanation for the left sided preponderance of the cleft. To this problem, it may be possible to assume that the left side of the embryonic upper lip may be more retarded in differentiation than the right side and the retardation on the left side may cause the side to suffer any influences of teratogenic factors for a longer period as compared with the opposite one. In the present study, there was no evidence to support that assumption, and to the author's regret, the results gave neither any explanation or any suggestion for the preponderance. Therefore, the truth still remains unknown.

Summary

1. The early development of the upper lip was examined in 113 human embryos.
2. The great part of the upper lip is completely developed at
horizon XIX (38-40 days) in almost all cases and at horizon XX (40-42 days) in all cases.

3. Although the side difference in development of the upper lip was observed during the early stage of its formation in several embryos, there found no consistency among them.

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References


Explanation of Plate I

Figs. 1-5 showing the standard contour of the upper lip in development at each horizon.

Fig. 1. Embryo at Horizon XVI. ×8.
Fig. 2. Embryo at Horizon XVII. ×8. Note the definite facial processes.
Fig. 3. Embryo at Horizon XVIII. ×8.
Fig. 4. Embryo at Horizon XIX. ×7.
Fig. 5. Embryo at Horizon XX. ×6.